13. The method of claim 12 wherein the molecules or compounds are selected from DNA molecules, RNA molecules, peptide nucleic acids, artificial chromosome constructions, peptides, transcription factors.

REMARKS

Claims 1-21 were originally filed and were subject to a Restriction Requirement. Applicants affirm election, with traverse, of original claims 1-13, corresponding to the invention of Group I. Applicants acknowledge and thank the Examiner for her reconsideration of the Restriction Requirement and examination of claims 1-13 on the merits. Claim 2 has been amended to delete SEQ ID NO:6. This amendment was made to expidite allowance of the claim in view of provisional rejections of the claim under 35 U.S.C. 102(e) and 101, double patenting. See instant Office Action, pp. 9-10. Applicants expressly do not intend to relinquish any subject matter relating to any other element of the claimed invention. Claim 8 has been amended to clarify the invention. In particular, step b) of claim 8 has been amended to recite "detecting hybridization complex formation, wherein complex formation indicates expression of the nucleic acid in the sample". Support for the amendment to claim 8 is found in the specification, for example, at p. 32, lines 11-19, which describes hybridization reactions and detection in both absolute and differential formats. Claim 8 has been further amended at step b) to correct antecedent basis for the phrase "nucleic acid" in the claim. Applicants do not believe that the amendments to claim 8 effect a narrowing of the scope of the claim. No new matter is added by these amendments, and entry of the amendments is therefore requested.

Information Disclosure Statement

The Examiner stated that the PTO-1449 form listing the cited references was not included in the filing, therefore the Examiner cannot make of record the submitted references. Applicant is invited to supply the required PTO-1449 form in response to this Office Action.

An examination of our files indicates that according to the return postcard (copy attached) the PTO-1449 form was submitted together with the Information Disclosure Statement and copies of the cited references on 3/15/01. However, for the Examiner's convenience, a copy of the PTO-1449 form is attached to this response.

35 U.S.C. § 101, Rejection of Claims 1-6 and 12-13

The Examiner has rejected claims 1-6 and 12-13 under 35 U.S.C. § 101 because the claimed invention is not supported by either an asserted utility or a well established utility. The Examiner stated

that the claims are drawn to polynucleotides encoding SEQ ID NO:1, compositions, vectors and host cells thereof, a method of producing a recombinant protein, and a method of detecting expression of the nucleic acid. The specification asserts that these polynucleotides are useful in the detection of colon disorders such as colon cancer and polyps. The specification states that the majority of patients having colon disorders comprising cancer or polyps showed downregulation of this gene (Table 1), that this downregulation is consistent with genes whose differential expression is associated with colon cancer. The Examiner stated, however, that the experimental data of Table 1 does not support this allegation. The Examiner stated that the $\log_2$ values given in column 1 of Table 1 include positive numbers (specifically, +0.14, +0.52, +1.04, +1.1, and +1.29) indicating a positive differential expression, e.g., upregulation of the gene. The Examiner stated that this does not indicate an adequate nexus between the asserted properties of the claimed polynucleotides and the evidence of record.

Applicants disagree that there is neither a well established or asserted utility for the claimed polynucleotides. The Examiner has not addressed the fact that the claimed polynucleotides are disclosed as encoding SEQ ID NO:1, a polypeptide clearly related to human intelectin by a high degree of sequence identity (88%), and that intelectin has been disclosed as likely functioning as part of an antimicrobial defense mechanism in paneth cells of the gut mucosa, which may also play a role in other gastrointestinal disorders as well, specifically chronic inflammatory bowel disease and colorectal cancer (see specification, at p. 3, lines 17-29). Thus a well established utility exists for the claimed polynucleotides that is independent of any asserted utility.

It is, however, also asserted that the claimed polynucleotides are useful as a diagnostic indicator for colon cancer and colon polyps based on the differential expression of the gene in a majority of patients with colon cancer or colon polyps (specification, at p. 10, lines 10-24). Specifically, it is disclosed that the gene is downregulated in a majority of patients with colon cancer or colon polyps compared with either a pool of normal colon tissues or matched with histologically normal tissue from the same patient. It was further disclosed that differential expression was considered significant only if differential expression represents at least a two-fold change in expression in diseased versus normal tissue, corresponding to a log base 2 value ($\log_2$ DE) of +/- 1.0. Based on this criteria, it was disclosed in Table 1 that 8 of 14 patients showed significant downregulation of the gene, while 3 of 14 patients showed significant up regulation. The experimental data therefore clearly supports Applicants allegation that the gene encoding ITL is significantly downregulated in a majority of patients with either colon cancer or colon cancer. The Examiner's statement that the experimental data of Table 1 somehow does not support this allegation is

therefore incorrect. Likewise, the Examiner's conclusion that an adequate "nexus" does not exist between the asserted properties of the claimed polynucleotides (e.g., diagnostic for colon cancer or polyps) and the evidence of record (Table 1) is also without foundation. The Examiner presents no evidence or sound scientific reasoning for disputing the inventor's conclusion that the downregulation of the gene for ITL in a majority of colon cancer or colon polyp patients provides a "substantial likelihood" that the polynucleotide would be a useful diagnostic indicator for these conditions. The Examiner is reminded that an applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The Examiner stated further that claim 2 is drawn to the polynucleotides of SEQ ID NOs:6 and 7 disclosed as particularly useful for producing transgenic cell lines or organisms. The specification asserts that expression of the transgene can be monitored by various means in transgenic animals before, during, and after challenge with experimental drug therapies (specification, p. 32, lines 11-13). The Examiner stated, however, that for the reasons set forth previously, the specification does not provide objective evidence that a nexus exists between the loss of expression of the nucleic acids encoding SEQ ID NO:1 and the presence of colon tumors or polyps, and therefore provides no objective evidence that restoration of expression of SEQ ID NO:2, 6 or 7 in tumor or polyp tissue can induce a normal phenotype in said tissues. The specification does not teach that the loss of expression of SEQ ID NO:1 is a cause of the malignant phenotype versus an effect of malignancy.

For the reasons discussed above, Applicants submit that an adequate "nexus" has been established between the reduced expression of ITL and the presence of colon cancer and colon polyps, and therefore that the use of non-human variants of SEQ ID NO:2 in transgenic animal models to test potential therapeutic or toxic agents as disclosed at p. 32, lines 11-13 of the specification is substantial, specific, and credible. However, the specification also teaches the use of the mammalian variants of SEQ ID NOs:6 and 7 "--- in hybridization, amplification, and screening technologies to identify and distinguish between SEQ ID NO:2 and related molecules in a sample" (specification, p. 11, lines 29-30). This asserted utility does not require a "nexus" between the expression of SEQ ID NO:6 or 7 and any disease state as it is unrelated to the screening or development of drugs.

The Examiner stated further that claims 12 and 13 are drawn to a method of using a cDNA to screen a plurality of molecules or compounds that specifically bind the cDNA encoding SEQ ID NO:1, comprising peptides, transcription factors, repressors and regulatory molecules. However, the Examiner stated, the specification does not assert a specific, substantial credible utility for said peptides,

transcription factor, repressors and regulatory molecules. The only function attributed to these generalized molecules and compounds is that they bind to the disclosed polynucleotides. This claimed subject matter is not supported by a specific, substantial and credible utility because the function of "binding" is generally applicable to a broad class of subject matter.

As the Examiner has noted, claims 12 and 13 are drawn to a "method of use" of the claimed polynucleotides, that is limited in scope to said polynucleotides, not to the peptides, transcription factors, etc., to be screened according to the method described. As such, the "utility" of the claimed invention is the ability to bind specifically to the claimed polynucleotides whose utility has been established as described previously. The means to measure specific binding is adequately disclosed in the specification, for example, at p. 9, lines 12-15, and in Example XV, p. 36. The claimed subject matter, a specific method of use of the claimed polynucleotides, for whom a specific, substantial, and credible utility has been established, is therefore also specific, substantial and credible, regardless of the fact that the function of "binding", per se, may be generally applicable to a broad class of subject matter.

Applicants therefore submit that both a well established as well as a specific and substantial, credible asserted utility is presented for the claimed polynucleotides, and therefore for their methods of use as well, and request withdrawal of the rejection of claims 1-6 and 12-13 under 35 U.S.C. § 101.

35 U.S.C. § 112, First Paragraph, Rejection of Claims1-6

The Examiner has also rejected claims 1-6 and 12-13 under 35 U.S.C. § 112, first paragraph, specifically since the claimed invention is not supported by either a asserted utility or well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants submit that to the extent the rejection is based on the unsupported rejection of these claims for lack of utility, the rejection under 35 U.S.C. § 112, first paragraph is similarly unsupported and should be reversed. Withdrawal of the rejection is therefore requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claim 7

The Examiner has rejected claim 7 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that claim 7 is drawn to a method of producing a protein by recombinant

expression of cDNA, however that Komiya et al. (BBRC, 1998) teaches that attempts to produce mouse ITL by recombinant expression failed due to a dramatic reduction in growth rates and no expressed protein was detected. The instant specification does not teach a method of producing a recombinant protein which would overcome this problem of toxicity.

An examination of the cited reference reveals that the lack of expression of ITL, specifically in E. coli, is the based on the apparent antimicrobial activity of ITL (see Komiya et al., p. 762). Since the specification describes numerous host systems other than microbial hosts for producing the protein by recombinant means (i.e., yeast, insect, plant cell, and animal cells; specification, p. 14, beginning at line 30), the specification does indeed teach methods of producing a recombinant protein which would overcome this problem of toxicity. Withdrawal of the rejection is therefore requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 2, 12, and 13

The Examiner has rejected claims 2, 12, and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) The Examiner stated that claim 2 is drawn in part to an isolated cDNA comprising SEQ ID NO:4 and 5, and that both SEQ ID NO:4 and 5 contain numerous "N" residues indicative of a undefined nucleotide residue. The specification does not teach that substitution of all of G, C, A, and T in place of the "N" residues would result in polynucleotides which would have the same use as the ITL polynucleotides of SEQ ID NO:1, nor does the specification teach a use for variant polynucleotides which would not function as claimed (emphasis added). The Examiner recited Regents of UC v Eli Lilly with respect to the holding of the court that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus (emphasis added).

Applicants strongly disagree that the cited polynucleotide sequences, SEQ ID NOs:4 and 5, are defined only by functional activity and would not function as claimed. The "numerous N residues" referred to by the Examiner in these sequences constitute 9/497 nucleotide residues for SEQ ID NO:4, or <2% of the total sequence, while for SEQ ID NO:5 they are 3/606 nucleotide residues, or <0.5% of the total sequence. It is therefore clearly unwarranted to allege that the sequences are not adequately described in structural terms to function as claimed, "to distinguish between SEQ ID NO:2 and related molecules in a sample"(specification, p. 11, lines 29-30). Applicants further submit that the sequences in

the Sequence Listing, including those with cited Ns, conform to CFR37 § 1.822 in which N is defined by reference to the tables in WIPO Standard St.25 (1998) Appendix 2, Tables 1 and 3.

Applicants also submit that the specification, at p. 10, line 10, as well as the Sequence Listing list the physical clones on which the sequences are based. Applicants reiterate that these clones identify actual biological material, cDNAs which were prepared as described in EXAMPLES I-III of the specification, from mRNAs expressed in a cDNA library.

Applicants further submit that even if it were not described in EXAMPLE III which states that, "(t)he cDNAs were prepared and sequenced by the method of (1975; J Mol Biol 94:441-448) using an ABI PRISM 377 sequencing system (Applied Biosystems) or the MEGABACE 1000 DNA sequencing system (APB)", a person skilled in the art would know that the nucleotide sequences of the Sequence Listing had been prepared by automated methods. In early publications of sequences, it was commonly known and accepted that a sequence prepared by these methods might contain occasional sequencing errors and unidentified nucleotides, but the physical clone was useful despite any unresolved base(s).

More recently, it has become standard practice for curators of databases to use N to mask those parts of sequences providing low information, such as repetitive elements, in order to optimize algorithmic searches for domains and motifs of far greater value. A recently issued Incyte patent, USPN 6,303,297, (filed 13 November 1997) states in column 11, lines 53-57, "Low information sequences, although not necessarily informative in comparative analysis, are a part of the actual sequence, and thus are masked in the edited sequence instead of removed so that the low information sequence can be obtained in the database if necessary. These sequences are masked by substituting an N for the actual nucleotide (i.e. G, A, T, or C). This masks the low information sequences for search purposes but preserves the spacing of the DNA molecule. The actual sequences corresponding to the masked sequences are stored for informational purposes." So Applicants still further submit that the Ns in the claimed sequences do not hinder their use by one of skill in the art in various methodologies commonly using either the physical clone or sequence.

In early sequencing technology or this late in the genomics race, a person skilled in the art would know that these sequences represent biological material, could be obtained from commercial sources or using PCR and a cDNA library, and if desired, any particular N could be resolved using standard recombinant or database methodologies Recombinant technologies are provided in Sambrook et al. and Ausubel et al. as cited in the DESCRIPTION OF THE INVENTION on page 14, lines 29 and p.15, line 1, respectively (earlier full references on page 12, lines 24-25, and p. 14, lines 4-5, of the specification), and

enabled in EXAMPLES II and XII of the specification. Commonly available assembly software and the sequences in the NCBI public databases may also be used to assemble the sequences and resolve Ns as enabled in EXAMPLE V of the specification.

Applicants submit that the specification demonstrates a strong association of the claimed polynucleotides encoding SEQ ID NO:1 with colon cancer and colon polyps, and that one skilled in the art would clearly know how to use the claimed polynucleotides, including SEQ ID NOs:4 and 5 in methods to diagnosis colon cancer or colon polyps, and to identify molecules related to SEQ ID NO:2.

(B) The Examiner also stated that claims 12 and 13 are drawn to a method of using a cDNA to screeen a plurality of molecules or compounds for binding the cDNA encoding SEQ ID NO:1, however that the specification has not provided a written description of the structure of specific peptides, transcription factors, repressors and regulatory molecules that bind the polynucleotides. As stated in the paragraph above, a description of functional activity only does not provide adequate written description of the genus.

Applicants reiterate that the claims are not drawn to "genus" of molecules or compounds, but rather to "method of use" of the claimed polynucleotides to identify molecules or compounds that specifically bind the polynucleotides. Therefore a written description of specific peptides, transcription factors, etc., to be screened in such a method is not required in order to enable one skilled in the art to use the invention comensurate with the scope of the claims, only that the method be adequately described as it is at p. 20 of the invention.

For all of the above reasons, Applicants submit that the subject matter of claims 2, 12, and 13 is adequately described in the specification to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed and request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, Second Paragraph, Rejection of Claim 8

The Examiner has rejected claim 8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claim 8(d) recites: "comparing hybridization complex formation with a standard, wherein the comparison indicates expression of a nucleic acid in the sample". The Examiner stated, firstly, that the method objective as stated in the preamble is to detect expression of a nucleic acid in a sample, not a cDNA. Furthermore, the Examiner stated, the claim does not incorporate the difference between the sample and standard in the final step, and is therefore indefinite. The Examiner

stated that for purpose of examination, the claim 8(d) will read as --comparing hybridization complex formation with a standard, wherein detection of a higher level of hybridization complex in the sample is indicative of expression of the nucleic acid--.

Claim 8 has been amended at step b) to replace "cDNA" with "nucleic acid". The claim has also been amended to recite the detection of nucleic acids hybridizing with the claimed polynucleotides of the invention in "absolute" rather than "differential" terms as described in the specification at p.32, lines 11-14. In particular, step b) of claim 8 has been amended to recite "detecting hybridization complex formation, wherein complex formation indicates expression of the nucleic acid in the sample". The claim, as amended, is therefore clear and definite without reference to comparison with a standard because, as recited at lines 13-14 of the specification, "signal strength correlates with mRNA levels in the sample". Withdrawal of the rejection is therefore requested.

35 U.S.C. 102(e), Rejection of Claim 2

The Examiner has rejected claim 2 under 35 U.S.C. § 102(e) as anticipated by Seilhammer et al. (09/540,212). Seilhammer et al. discloses the polynucleotide of SEQ ID NO:65953 which is identical to the instant polynucleotide of SEQ ID NO:6 as claimed. The Examiner stated that the rejection may be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the same inventor of this application and is thus not the invention "by another", or by an appropriate showing under 37 CFR 1.131.

SEQ ID NO:6 has been deleted from the claim. Withdrawal of the rejection is therefore requested.

35 U.S.C. § 101, Double Patenting, Rejection of Claim 2

The Examiner has provisionally rejected claim 2 under 35 U.S.C. § 101, as claiming the same invention as that of claim 1 of copending Application Serial No. 09/540,212. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The Examiner further stated that since the two applications are commonly assigned, the issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved. Since the PTO will not institute an interference between applications of common ownership (See MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter.

The amendment to claim 8 deleting SEQ ID NO:6 has been discussed supra. Withdrawal of the

provisional rejection of the claim under 35 U.S.C. § 101 for double patenting is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record indicted below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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Date: July 3, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 2 and 8 have been amended as follows:

2. (Once Amended) An isolated cDNA comprising a nucleic acid sequence selected from:

a) SEQ ID NO:2 or the complement thereof;

b) a fragment of SEQ ID NO:2 selected from SEQ ID NOs:3-5 or the complement thereof; and

c) a variant of SEQ ID NO:2 [selected from] comprising SEQ ID NO[s]:[6-]7.

8. (Once Amended) A method for using a cDNA to detect expression of a nucleic acid in a sample comprising:

a) hybridizing the composition of claim 4 to nucleic acids of the sample under conditions to form [thereby forming] at least one hybridization complex[es]; and

b) detecting [comparing] hybridization complex formation [with a standard], wherein complex formation [the comparison] indicates expression of the nucleic acid [cDNA] in the sample.

Commissioner for Patents
Washington, D.C. 20231

Mailed: 03/15/01
Docket No.: PC-0027 US

Applicants: Yue et al.
Serial No.: 09/771,503
Filing Date: January 26, 2001
Title: **INTELECTIN**

Enclosed are the following:
1. Return Postcard;
2. Information Disclosure Statement (2 pp., in duplicate);
3. List of References Cited - (Form PTO-1449) (1 pg.); and
4. Copies of Eleven (11) references cited.

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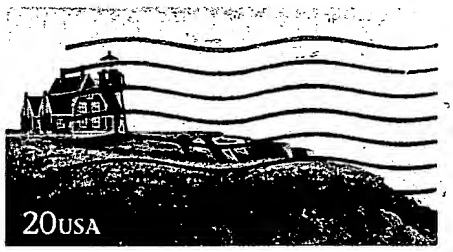

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